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Haloperidol and Apomorphine Effects on Ethanol Reinforcement in Free Feeding Rats

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PFEFFER, A. O. AND H. H. SAMSON. *Haloperidol and apomorphine effects on ethanol reinforcement in free feeding rats.* PHARMACOL BIOCHEM BEHAV **29**(2) 343–350, 1988.—Free feeding male Long Evans rats were trained to lever press on a Fixed Ratio 8 schedule for 10% ethanol reinforcement. Mean ethanol intake in 30-minute sessions was 0.38 g/kg. Subcutaneous apomorphine (APO: 0.025 to 0.5 mg/kg) and haloperidol (HAL: 0.005 to 0.0625 mg/kg) administered 15 minutes before sessions dose-dependently reduced responding, but only APO reduced momentary response rates. Low doses of HAL reduced the effect of 0.3 but not 0.05 mg/kg APO. When the rats were food-restricted, control response rates decreased, and APO (0.025 and 0.05 mg/kg) had no further effect. Results were discussed in terms of dopamine involvement in the mechanism of ethanol reinforcement.

Ethanol Apomorphine Haloperidol Dopamine Self-administration Reinforcement Rats

STUDIES of various aspects of alcohol reinforcement in an animal model have been hampered by the fact that the taste of alcohol is initially unpalatable to animals that are not genetically selected to prefer alcohol [19,25]. High levels of voluntary ethanol intake have only been obtained either with some level of concurrent food-restriction or following extensive food-restriction [2]; as ethanol is a source of calories as well as an intoxicant, this makes determination of its reinforcing properties difficult. In the past few years, several new methods for initiating ethanol-reinforced responding by free feeding rats have been developed in this laboratory [10, 11, 25, 26]. With these new methods, it is now possible to study ethanol reinforcement in an animal model that is closer both to the human drinking situation and to other types of noncaloric drug reinforcement.

A current idea regarding the brain neurochemical substates of reinforcement in general is the dopamine (DA) hypothesis of reward [30, 31, 34]. It has been proposed that activation of the mesolimbic DA pathway, projecting from the ventral tegmental area of the brainstem (A10) to the nucleus accumbens, plays a necessary part in the reinforcing effects of a variety of stimuli, including food and water, stimulant and opiate drugs, and electrical brain stimulation [32]. The case for DA involvement in alcohol reinforcement has remained controversial, and norepinephrine (NE) is considered by some researchers to be more directly involved than DA [1,17]. While there is no reason that both catecholamines, as well as many other neurotransmitters, may not be necessary for the manifestation of ethanol reinforcement, it was not possible until recently to evaluate DA's role by the operant technology used in the study of other reinforcers. Using the new methodology, we have begun to look at the question of DA involvement in ethanol reinforcement.

We have found that pimozide (PIM), a specific DA-receptor blocker, reduces operant responding reinforced by alcohol in both food-deprived and free feeding rats, and also reduces home-cage ethanol drinking [21,22]. It has been argued that response-reduction following DA antagonists may reflect impaired ability to respond due to extrapyramidal motor effects [7]. The finding of reduced drinking using the relatively undemanding licking response is consistent with other research suggesting that at least part of the response decrement is motivational in origin [14,22]. We also found that d-amphetamine (DEX), an indirect DA and NE agonist, has differential effects depending on whether the rats are food-deprived or not [20,21]. Only in the food-deprived condition does a low dose of DEX increase responding; in both conditions moderate doses decrease responding. The response-decreasing effects of DEX were increased rather than diminished, by PIM, but since the PIM doses employed decreased responding when given alone, this experiment was judged inconclusive with regard to the DA mediation of the DEX effect.

In the present experiment, the effects of a specific and

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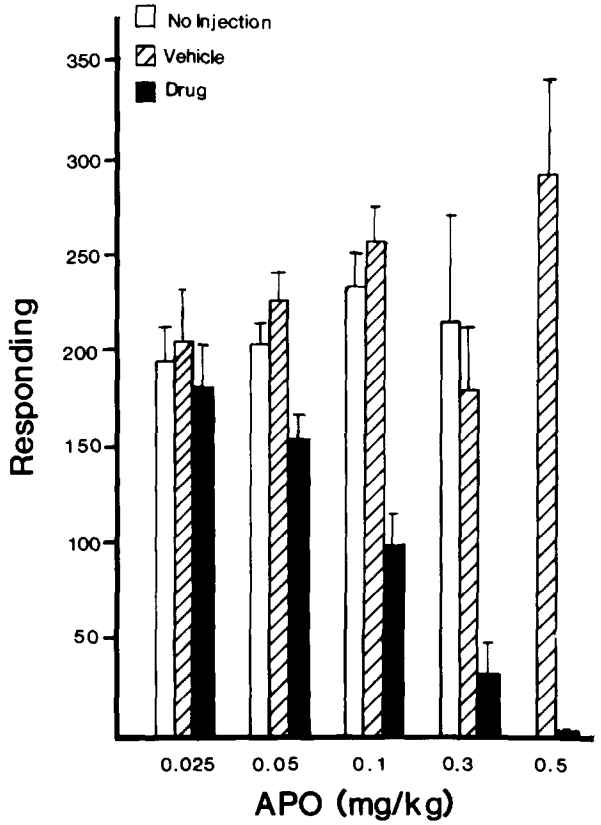

FIG. 1. Effect of APO on mean (+s.e.m.) lever pressing in 30-minute sessions by free feeding rats, reinforced by 0.1 ml 10% ethanol on an FR8 schedule.

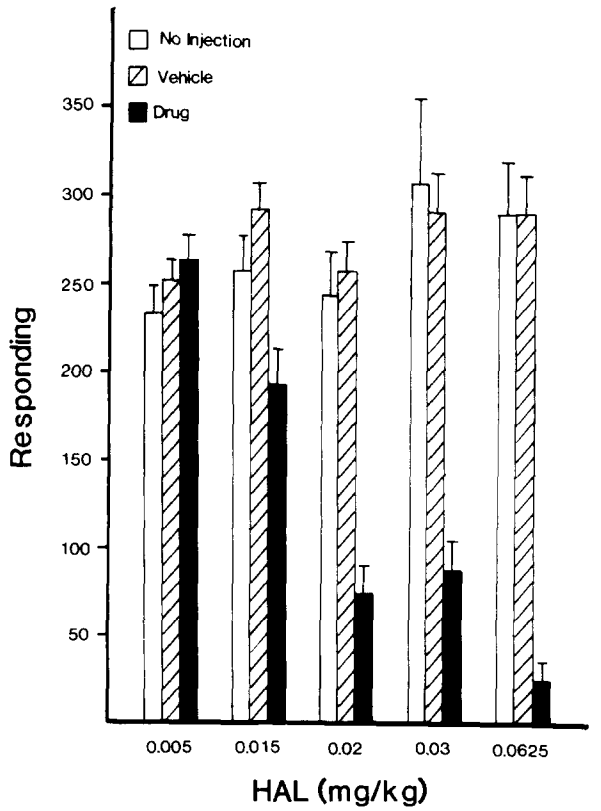

FIG. 2. Effect of HAL on mean (+s.e.m.) lever pressing in 30-minute sessions by free feeding rats, reinforced by 0.1 ml 10% ethanol on a FR8 schedule.

direct DA agonist, apomorphine (APO), were examined along with a second DA antagonist, haloperidol (HAL). A dose effect curve was obtained for each drug, and then an effective dose of APO was given in conjunction with two subthreshold doses of HAL and one of PIM. For comparison with DEX, the rats were also food-restricted and given low doses of APO.

METHOD

Animals

Ten male Long Evans rats, obtained from the University of Washington's Department of Psychology vivarium, were individually housed in standard hanging cages. Artificial lighting was on from 0700 to 1900 hours, and temperature and humidity were kept within NIH specifications. At the start of the experiment, the rats were 60 days old, and their weights ranged from 262 to 368 g (mean=308.5, SD=36.3). They were maintained on ad lib food (Purina and Wayne Rat Chow) and water, except as described below.

Apparatus

The operant chambers have been described in detail before [24]. Briefly, each box contained two removable levers mounted on one wall and two 0.1 ml capacity dippers situated lateral to each lever on the same wall. Completion of a specified number of responses on a lever resulted in activation of the adjacent dipper for three seconds. In the present experiment, only the lever and dipper closest to the front of the chamber were used, with the other lever removed. The chamber was lighted by a 1 watt house light during the session. Response contingency control and data acquisition were with Apple microcomputers.

Drugs

Apomorphine (Sigma) was dissolved in 0.9% saline. Haloperidol (Haldol, McNeil Pharmaceutical) was diluted with 0.9% saline. Pimozide (McNeil Pharmaceutical) was first dissolved in a few drops of acetic acid, and then diluted with 5% (w/v) sucrose. As all injections were subcutaneous, concentrations were varied to keep injection volumes between 0.1 and 0.2 cc. Control injections were of 0.9% saline for APO, 0.9% saline with pH adjusted to 3 for HAL, and 5% sucrose with a few drops acetic acid for PIM.

Procedure

After two days adjustment to their new housing situation and three days handling, the rats were trained to lever press for 20% (w/v) sucrose, using the method of successive approximations. During this initial shaping, food was restricted for from 3 to 5 days. After this time, except during the weight-reduction condition described below, food and water were freely available in the home cages. Sessions lasted 30 minutes and took place at the same time each day. When lever pressing was reliable, response requirement was gradually brought up to a Fixed Ratio 8 (FR8). After a week

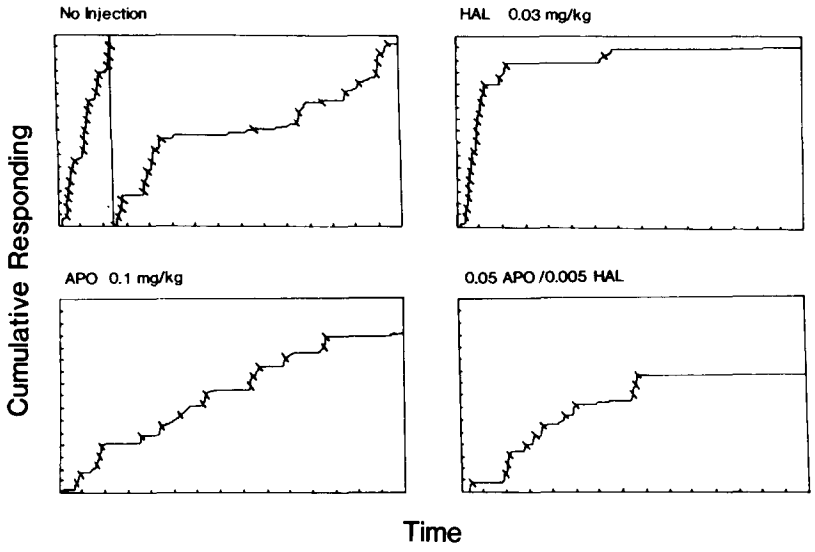

FIG. 3. Sample cumulative records for rat APO 8 in free feeding condition. Grid=10 responses by 2 minutes. Slashes indicate reinforcement.

of FR8 with 20% sucrose reinforcement, 5% ethanol (v/v) was substituted for the 20% sucrose. For 4 rats, 10% ethanol was substituted for 5% ethanol after another week. To maintain responding by the remaining 6 rats, it was necessary to present a mixture of sucrose and ethanol and more gradually (over the course of 6 more weeks) to reduce the sucrose and increase the ethanol to a final concentration of 10% ethanol, 0% sucrose. Two rats were discarded for low responding during this stage of training, and a third was discarded when responding deteriorated following equipment failure.

After responding had stabilized, injections were initiated. For the first two weeks, saline was injected to accustom the rats to the injection procedure. After this, two injections were given each week, vehicle on one day, and drug on the following day. The dosage sequence, in mg/kg, was as follows. APO: 0.05, 0.025, 0.10, 0.025, 0.05, 0.10; HAL: 0.0625, 0.015, 0.03, 0.02; APO+HAL: 0.05+0.01, 0.05+0.005; APO: 0.05; PIM: 0.0625; APO+PIM: 0.05+0.0625; HAL: 0.005. APO and HAL were injected 15 minutes before sessions, and PIM was injected 30 minutes before sessions. After the last of these injections, one rat was removed from the experiment because of a tumor, and the remaining rats were put on a restricted food regime and reduced to 80% of their free feeding body weights over the course of two weeks. They were maintained at these weights for two more weeks, during which APO (0.025 and 0.05 mg/kg) was injected, one drug and one vehicle injection each week. The rats were then returned to ad lib feeding and simply maintained in their home cages for two months, with no further access to alcohol. Finally, operant sessions were resumed for four rats, responding was allowed to restabilize, and in the last two weeks of the experiment, two higher APO doses, 0.3 and 0.5 mg/kg, were given, along with the appropriate vehicle injections.

Data Collection and Analysis

Responding in time was registered by the computer for the later generation of cumulative records. These data were stored on floppy disk along with response and reinforcement totals. Drug effects on response totals were evaluated first with ANOVA for repeated measures. A separate ANOVA compared each dose to its vehicle session and the preceding day's no injection session, to take into account fluctuation in control responding over time. Significant results were further analyzed with paired Bonferroni t-tests. Independent t-tests for unequal n's and assuming unequal variance were used to make comparisons between the effects of different drugs and drug combinations, and to look at the effects of food-deprivation.

RESULTS

In the week before injections were begun, mean weight was 515.2 g (SD=40.9). Mean responding per 30-minute sessions during that week was 196.6 (SD=56.6), which corresponded to a mean intake of 0.38 g/kg (SD=0.12).

Response means for the APO injections are presented in Fig. 1. The lowest dose (0.025 mg/kg) did not significantly affect responding. The 0.05 mg/kg dose reduced responding to 71.9% of vehicle responding [s.e.m.=7.1, $t(19)=5.299$, $p<0.01$]; 0.10 mg/kg reduced responding to 37.1% of vehicle [s.e.m.=5, $t(13)=11.406$, $p<0.01$]; 0.3 mg/kg reduced responding to 16.5% of vehicle responding [s.e.m.=8, $t(3)=5.228$, $p<0.05$]; and 0.5 mg/kg reduced responding to 0.6% of vehicle [s.e.m.=0.55, $t(3)=5.921$, $p<0.01$]. Because of an error, there was no noninjection control session for the last dose. The 0.05 mg/kg dose was given a third time to see if sensitivity to the drug was altered by the HAL injections, and no change was found.

Figure 2 presents means for the HAL series. The lowest dose (0.005 mg/kg) did not significantly affect responding (for all rats except one, responding was slightly elevated following this dose). For the next dose (0.015 mg/kg), although the F was significant, $F(2,12)=3.952$, $p<0.05$, none of the paired comparisons reached significance at the 0.05 level. Responding after this dose was 81.6% (s.e.m.=16.6) of responding after vehicle. After one extreme score was eliminated (176.1%), this figure fell to 65.8% (s.e.m.=6.3). Without this score, responding after HAL was significantly lower than

TABLE 1

APO AND HAL EFFECTS ON PATTERN OF RESPONDING MEANS (±SEMS)

Drug Condition	Dose (mg/kg)	Resp. Rate (resp/min)	Total Resp. (% of control)
APO	0.025	34.7 (4.8)	100.4 (14.8)
	0.050	26.6 (3.0)	71.9 (7.1)
	0.100	19.6 (3.2)	37.1 (5.0)
HAL	0.005	56.7 (10.2)	106.9 (8.0)
	0.015	51.5 (5.1)†	65.8 (6.3)
	0.02/0.03‡	42.6 (7.2)*	28.9 (3.8)
APO+HAL	0.05+0.005	19.2 (4.0)	35.6 (6.3)
	0.05+0.01	23.4 (4.8)	29.6 (6.4)
No Inj.		45.7 (2.8)	
Vehicle		47.1 (2.2)	

*Significantly different from 0.1 mg/kg APO ($p<0.05$).
†Significantly different from 0.05 mg/kg APO ($p<0.01$).
‡The 0.02 and 0.03 HAL doses were grouped together as they were not significantly different from each other.

after vehicle, $t(5)=5.146$, $p<0.01$. The 0.02 mg/kg dose reduced responding to 27.9% of vehicle responding [s.e.m.=6.0, $t(5)=11.536$, $p<0.01$]; 0.03 mg/kg reduced responding to 30% of vehicle responding [s.e.m.=5.12, $t(5)=9.962$, $p<0.01$]; and 0.0625 mg/kg reduced responding to 7.7% of vehicle responding [s.e.m.=3.7, $t(6)=12.300$, $p<0.01$].

Cumulative records for one representative rat are presented in Fig. 3 for drug and control responding. As illustrated by these examples, responding after HAL generally started out at a normal high rate, but terminated earlier than in control sessions, while responding after APO was more sporadic throughout the session. These observations were verified statistically. "Early-session" (below) refers to the first half of the reinforcers earned, starting with the first reinforcer earned, rather than with the start of the session. Judgment was exercised in the application of these cut-off points, however, when they happened to precede or follow long pauses in responding. In terms of either response totals or percent suppression, the 0.05 APO and the 0.015 HAL effects were not significantly different from each other, but when early-session momentary response rates were compared, the APO rates were significantly lower than the HAL rates, $t(12)=4.226$, $p<0.01$. Likewise, when the 0.10 APO response totals and percent suppression were compared to 0.02 and 0.03 mg/kg HAL response totals and percent suppression, there was no difference, but early-session response rates after APO were again lower than after HAL, $t(13)=2.914$, $p<0.05$. (As 0.02 and 0.03 HAL were not significantly different from each other, they were lumped together for this analysis.) Higher HAL and APO doses reduced responding to levels too low to yield meaningful estimates of response rates; only sessions in which at least 5 reinforcers were earned were considered in this analysis. The response totals after the lowest dose of HAL were significantly higher than after the lowest dose of APO, but initial response rates did not differ. Table 1 presents early-session mean response rates (responses/minute) for the various drug and control conditions.

The drug combination response means and their controls

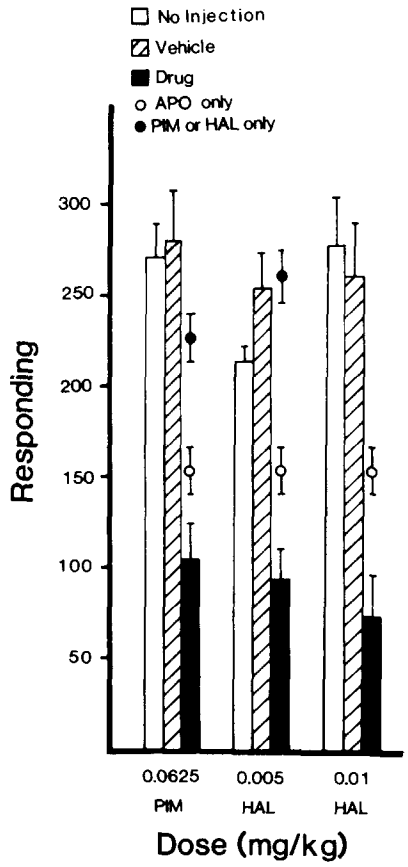

FIG. 4. Effect of HAL and PIM coadministered with 0.05 mg/kg APO on mean (+s.e.m.) lever pressing in 30-minute sessions by free feeding rats, reinforced by 0.1 ml 10% ethanol on a FR8 schedule.

are shown in Fig. 4. All three combinations reduced responding compared to vehicle control. The 0.05 APO/0.005 HAL combination reduced responding to 35.6% of vehicle [s.e.m.=6.3, $t(5)=9.717$, $p<0.01$]; for this dose the difference between vehicle and no injection sessions was also significant. The 0.05 APO/0.01 HAL dose reduced responding to 29.6% of control [s.e.m.=6.4, $t(5)=6.663$, $p<0.01$], and 0.05 APO/0.0625 PIM reduced responding to 36.7% of control [s.e.m.=5, $t(5)=7.667$, $p<0.01$]. Compared to 0.05 mg/kg APO alone (Fig. 5), both HAL combinations were significantly lower, but the PIM combination was not [HAL 0.005: $t(15)=2.812$, $p<0.05$; HAL 0.01: $t(17)=4.059$, $p<0.01$]. The PIM dose alone produced no significant effect on responding.

Figure 6 shows the APO effects after the rats were reduced to 80% of their free feeding body weights by food restriction. During the last three days before food restriction, the rats responded on average of 246.6 times per 30-minute session (s.e.m.=8.6), which corresponded to an ethanol intake of 0.43 g/kg (s.e.m.=0.02). After food restriction, they responded on average 167.8 (s.e.m.=13.8) times, which corresponded to 0.35 g/kg (s.e.m.=0.03). Although neither the decrease in responding nor the decrease in g/kg was significant, early-session momentary response rates were significantly decreased by food restriction, $t(51)=6.607$, $p<0.001$]. Figure 7 gives an example of one rat's response pattern, which illustrates behavior of the group. This disruption in response pattern appeared in the

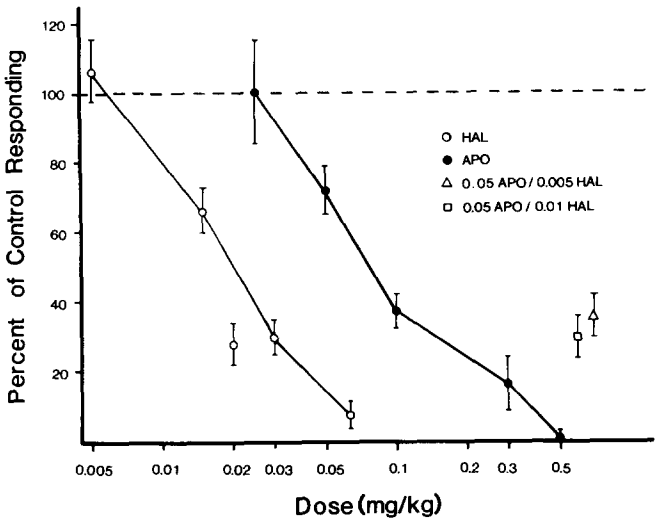

FIG. 5. Dose-effect curves for HAL and APO on responding (mean±s.e.m.) as % of responding after control injections. HAL curve does not include 0.02 mg/kg dose as its effect may have been affected by dose sequence (see the Discussion section). Effect of combined APO and HAL doses is shown to right of dose-effect curves.

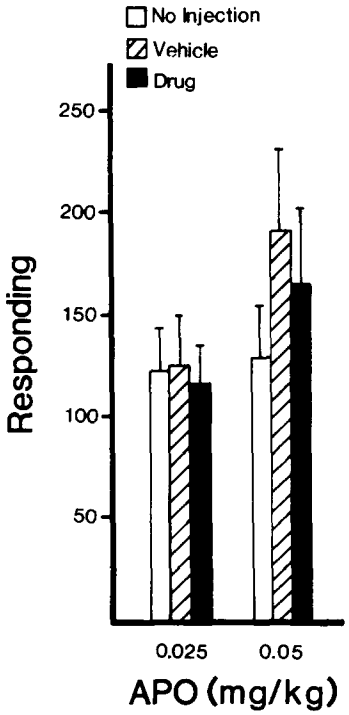

FIG. 6. Effect of APO on mean (+s.e.m.) lever pressing in 30-minute sessions by food-restricted rats, reinforced by 0.1 ml 10% ethanol on a FR8 schedule.

very first session (on the third day) following the start of food restriction, when their weights had only dropped to an average of 90.3% (s.e.m.=8.6) of free feeding weights. In the food-restricted rats, neither dose of APO (0.025 and 0.50 mg/kg) produced a significant effect on response totals or early-session response rates.

DISCUSSION

There were five main findings in the present study. The first two are that both APO, a direct DA receptor agonist, and HAL, a direct DA receptor antagonist, decrease operant responding reinforced by 10% ethanol in free feeding rats. Third, although the effect on response totals is similar for the two drugs, effect on pattern of responding is dissimilar, with responding after HAL following a normal pattern in the first part of the session, but terminating earlier, and responding after APO disrupted from the beginning. Fourth, the 0.05 mg/kg APO effect was not antagonized by low HAL doses, although in an additional preliminary study (see Table 2), the effect of a higher APO dose was reduced by 0.005 mg/kg HAL. Finally, in conjunction with these particular pharmacologic and behavioral histories, the effect of food deprivation was to disrupt operant responding, rather than to increase it as has been reported in the past.

APO was given in the present experiment partly in order to compare its effects to those previously obtained with DEX. Those effects were to reduce responding at medium doses in both food-restricted and free feeding animals, and to increase responding at low doses in food-restricted rats [20,21]. Since DEX indirectly activates both NE and DA receptors by facilitating the release of these catacholamines [8,9], it was not clear whether DA or NE or their combination were responsible for these effects. The present finding that APO, a specific DA agonist, produced the same effect as DEX on free feeding rats is consistent with dopaminergic involvement in this DEX effect as well.

We were not able to complete the comparison of the low dose effect of the two drugs on food-restricted rats, however, as the effect of food-restriction on baseline responding was different in the present experiment compared to the DEX experiment [21]. In the previous experiment, responding was significantly elevated by food-restriction. This effect was expected, and while it might be attributed to the increased reinforcing effect of the calories provided by alcohol, increased responding has been seen by others using noncaloric drug reinforcement [4]. It is difficult to explain the lack of such an increase in the present experiment. While drug history may have somehow altered the effect of food-deprivation, another possibility is that the ethanol-initiation procedure used in the present study resulted in this difference. In the previous study, the rats had been initiated to ethanol reinforcement by a "secondary-conditioning" procedure [12], in which licking 5% ethanol from a drinking spout was an operant reinforced on an FR 20 by presentation of a dipper filled with either 20% sucrose or with 5% ethanol. We are currently investigating the long-term effects of several different ethanol-drinking initiation procedures, and may eventually be able to answer this question.

The decrease in ethanol-reinforced responding caused by HAL extends our previous findings with PIM [21,22], also a dopamine receptor antagonist. While PIM is at least as specific a DA blocker as HAL [5], the finding that both drugs produce the same effect increases our confidence in the dopaminergic mechanism of these results. A subthreshold PIM dose was chosen in the present experiment because it was thought that the failure of PIM to antagonize the effects of DEX in our previous study might have been attributable to too high a PIM dose. (However, see discussion of drug interaction below.) This subthreshold dose of PIM did not significantly change the APO effect, but as the drug was ad-

TABLE 2

APO AND HAL EFFECTS ON MEAN (±SEM) RESPONDING REINFORCED WITH 10% ETHANOL (N=3)

Drug	No Inj.	Veh. Inj.	Drug Inj.	
HAL (0.005)	139.3 (6.4)	100 (12.2)	105 (19.8)	NS
HAL (0.02)	127 (6.4)	117.8 (16.1)	98.6 (10.1)	NS
APO (0.3)	120.2 (25.4)	127.2 (13.7)	4.3 (2.0)	†
APO + HAL (0.3 + 0.005)	118 (15.9)	123.8 (15.8)	39.5 (8.6)	‡

Injections were given in this order (in mg/kg): 0.005 HAL, 0.3 APO, 0.005 HAL + 0.3 APO, 0.3 APO, 0.005 HAL + 0.3 APO, 0.02 HAL, 0.02 HAL. Five weeks before the first injection, these 3 rats had received 6 injections each of the benzodiazepine partial inverse agonist RO15-4513 (0.1 to 3 mg/kg) and 2 injections of 10 mg/kg chlordiazepoxide in another experiment [27]. In all other respects, procedural details were as described in the present experiment.

NS: Not significantly different from vehicle.

*Significantly different from vehicle ($p<0.05$).

†Significantly different from vehicle ($p<0.01$).

‡Significantly different from 0.3 mg/kg APO alone ($p<0.05$).

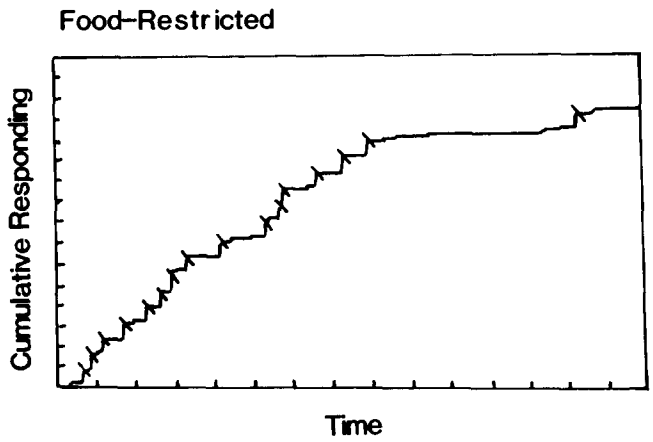

FIG. 7. Sample cumulative record for rat APO 8 in food-restricted condition. Grid=10 responses by 2 minutes. Slashes indicate reinforcement.

ministered only 30 minutes before the session, lack of effect may have been due to failure of the drug to reach peak effectiveness [16].

The HAL dose-effect curve is curious, in that there was no difference between the 0.02 and the 0.03 mg/kg effects. The explanation for this finding may lie in an order effect. It has been noted that a second administration of the same neuroleptic dose may have a larger effect on operant behavior than the first [34]; this has been seen as a learning phenomenon, and taken as further evidence of the similarity between the neuroleptic effect and extinction. Further analysis of our previous experiments on PIM's effect on alcohol reinforcement [21,22] shows that for all except one rat in each experiment, the second trial at the highest dose was more effective than the first, although when a third trial was given [22], this trend did not continue. In the present experiment, the higher dose was given the week before the lower, which may have increased the effectiveness of the latter compared to what it would have been in naive rats. A floor effect probably is not the explanation, as 0.625 mg/kg HAL produced a still greater reduction in responding. The lack of effect of 0.02 mg/kg HAL in a preliminary study with three additional rats (Table 2), who had never received a higher HAL dose, is consistent with the idea that exposure to higher doses may have some sort of sensitizing effect, but these results must be treated with caution because these three rats had a different drug history. Without further replication and experimentation, the learning interpretation remains speculative.

The normal early-session pattern of responding produced by HAL in the present experiment has been noted by other researchers using other neuroleptics and other reinforcers [31], and is consistent with the idea that the response decrement is due to an effect on reinforcement, rather than motor systems. The interpretation is that after a number of reinforcers (on some schedules secondary, rather than primary, reinforcers) have been experienced by the rats, the diminished reinforcing capacity, due to dopamine blockade, fails to maintain responding. This effect results in a normal, high rate of responding in the beginning of the session, which would be unlikely to occur if the rats were experiencing motor impairment, followed by early termination of responding. The possibility might be raised that such an effect is a temporal artifact and depends on the 15-minute interval between drug-administration and the start of the session. This is unlikely to be the explanation, however, as within-session increases in drug-effect have been observed in different operant situations both with PIM given four hours before sessions, and HAL two hours before sessions [16]. PIM's effect on many different measures has a slow onset but long duration, while the HAL effect generally peaks within one hour.

This response pattern is quite different from that seen after APO administration, where responding is generally slower and more sporadic from the start of the session. There is evidence that at 0.05 mg/kg, APO decreases release of DA in the nucleus accumbens, and decreases such behaviors as grooming, locomotion and rearing, probably through a presynaptic mechanism [15]. Doses of ethanol (0.025 and 0.50 g/kg) comparable to those ingested in the present study stimulate these behaviors, as well as DA release in the accumbens; these ethanol effects are blocked by 0.05 mg/kg APO. Thus the sporadic response pattern generated by the

lower APO doses (0.05 and 0.10 mg/kg) may reflect a combination of sedation and blockade of part of the alcohol effect, possibly the reinforcing part. There was too little responding after the higher doses to clearly categorize response patterns, but in this range APO is behaviorally activating [28], and competing behaviors could have interfered with responding. Alternatively, it could be that at higher (postsynaptic) doses, APO activates a critical "reward-sensitive" subset of DA receptors, rendering further ethanol ingestion redundant. APO, like amphetamine, is self-administered by rats [2].

When two drugs are homergic, i.e., have the same effect on a given dependent variable, like APO and HAL in the present experiment, there are several ways of evaluating their independence or interaction when given in combination [18,35]. The simplest is in terms of "effect-additivity." The separate effects of relevant doses of the two drugs are simply added together; if the observed effect of combining the two drugs is equal to this sum, the drugs are probably acting independently. In terms of effect-additivity, the combined effects of 0.05 APO and either 0.005 or 0.01 mg/kg HAL were clearly supraadditive, which suggests a facilitatory interaction. However, the "dose-additivity" model of independence is preferred to effect-additivity with drugs that may affect the same receptors, as dose-additivity predicts the results of combining different doses of the same drug. To use the dose-additivity model, dose-effect curves of the two drugs must first be obtained. Then, using the present data as an example, if the APO effect preceded the HAL effect, one would add 0.005 HAL to the dose of HAL that would produce the same effect as 0.05 APO alone; the effect that this sum would have (according to HAL's dose-effect curve, Fig. 5) is the prediction of the dose-additivity model. If HAL were faster acting than APO, then one would add 0.05 mg/kg APO to the APO dose that would produce the same effect as 0.005 mg/kg HAL, and if the two drugs acted synchronously, an average of these two figures could be used. The problem in the present case is that, if the effect of each dose is influenced by the rats' previous experience with higher doses, then it is unclear exactly what the true dose-effect curve of HAL is. It does not appear, however, that there was any clearcut antagonism of effect (which would be indicated by infraadditivity) when 0.05 mg/kg APO was combined with low doses of HAL; whether the drugs acted synergistically or independently remains for further research to determine. The results of the preliminary study displayed in Table 2 indicate that the effect of a higher (0.3 mg/kg) APO dose was antagonized by 0.005 mg/kg HAL, a dose too low to have any overt effect by itself. At 0.3 mg/kg, APO's main effect is thought to be at postsynaptic receptors, while the lower doses probably acted preferentially on autoreceptors, decreasing release of DA. Reanalysis of the combined effects of PIM and DEX in our earlier study [21] in terms of dose-additivity suggests that they were infraadditive. This would indicate partial antagonism, but all dose combinations except the highest, where there may have been a floor effect, were supraadditive when evaluated by effect-additivity. Thus this reassessment of the earlier experiment sheds no further light on the DA mediation of the DEX effect.

It has been assumed by many that a decrease in reinforcement value should be reflected in decreased responding and, conversely, that facilitation of reinforcement would lead to increased responding. In fact, the catecholamine theory of reinforcement had its origin in this interpretation of the "facilitating" effects of amphetamine on brain stimulation reward [29]. However, after low doses of neuroleptics, responding for both amphetamine [36] and cocaine [6] actually increases, presumably to compensate for the reduced effectiveness of these indirect DA agonists. In the present experiment, higher early session response rates after HAL compared to control sessions (Table 1) were not statistically significant. Another kind of compensatory change in responding would be a satiety-induced response decrement, and the haloperidol response patterns do resemble patterns seen when higher concentrations of alcohol (15 to 40%) are presented as reinforcement in the present initiation procedure [26]. Thus the a priori prediction of initial increases or decreases in responding as a consequence of increases or decreases in reinforcement value is debatable, although eventually, if reinforcement is sufficiently reduced, extinction of responding should occur.

Complementing the present paradigm, in which DA agonist and antagonist effects on operant behavior are examined, is the evidence that DA agonists are reinforcing in their own right. Amphetamine and cocaine are both abused by humans; amphetamine, cocaine and apomorphine are self-administered by rats [2, 6, 36]. No one, to our knowledge, has found neuroleptics to be abused by humans or self-administered by animals. Also, neuroleptics are reported to diminish amphetamine euphoria in humans [13]. Thus, it seems reasonable to assume that the decreases in responding following HAL in the present study are not due to an enhancement of ethanol's reinforcement value.

In conclusion, ethanol-reinforced operant responding in free feeding rats was reduced both by the direct DA agonist APO and by the DA antagonist HAL. Whatever the ultimate significance of DA's role in reinforcement, at this link in the chain leading from the ingestion of alcohol to its reinforcing effect upon behavior, alcohol seems to be no different from other reinforcers.

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